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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,209	07/05/2005	Maria Alessandra Alisi	274158US0PCT	7651
22850	7590	01/16/2009	EXAMINER	
OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			CHANG, CELIA C	
			ART UNIT	PAPER NUMBER
			1625	
			NOTIFICATION DATE	DELIVERY MODE
			01/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/541,209	Applicant(s) ALISI ET AL.	
	Examiner Celia Chang	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 04 November 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) 36-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/4/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Response filed by applicants dated Nov. 4, 2008 have been entered and considered carefully.

Claims 36-39 stayed withdrawn from consideration. Claims 1-35 are pending.

2. Applicants correction on the patent number Suzuki being US 6,096,746 is noted. The inadvertent typographical error is hereby corrected and made of record by the new PTO-1449.

3. The rejection of claims 1-35 under 35 USC 103(a) over Catlow et al. US 5,654,320 in view of Suzuki et al. '746 and Schaus et al. is maintained for reason of record.

The gist of applicants' argument is that

a) Catlow '320; Suzuki '746 and Schaus are for treating gastrointestinal disorders while the instant claimed compounds are analgesic;

b) the biological activities or potencies among the different species in the different references are different when Markush variables are introduced.

It is erroneous for applicant to misinterpret the references that the compounds were active *only in* treating gastrointestinal disorder. As it was clearly delineated in the previous office action that the references are indazolyl-piperidinyl compounds which have "5HT4" receptor modulating activity. Although 5HT4 receptor modulation can be useful in treating gastrointestinal disorder, it is also useful in treating pain (see Catlow '320 col. 19, line 21). Therefore, all references are analogous art with each other and with the instant application.

Further, some variation among the different Markush variable compounds showed differences in activity or potency which is expected since different compounds ordinarily incur difference in conformation thus binding activity. However, difference is *not* unexpected or unobvious. It has been clearly set forth by the court that "...thus motivation-suggestion-teaching test asks not merely what references disclose, but whether person of ordinary skill in the art possessed with understandings and knowledge reflected in prior art and motivated by general problem facing inventor, would have been led to make claimed combination..." In re Kahn 78 USPQ2d 1329. In the instant case, the variations around the central piperidinyl moiety and

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linkers have been clearly indicated by the prior art to be a region that has flexibility in modification. Successful modifications with linker length, on either side of the piperidinyl ring and ring rotation have been *repeatedly demonstrated* by species attributing to biological activity. As it was clearly delineated in the previous office action that:

" the indazolyl-linker-piperidinyl-linker-phenyl scaffold has been established for 5HT4 receptor and the tolerance of linker length, ring variation and substituents have also been well correlated with the binding activity (see Schaus et al. whole article). The teaching, suggestion and motivation for one skilled in the art to pick and choose the known attributes among the successful compounds is prima facie obvious design choice".

Absolute predictability is not required in establishing a prima facie case of obviousness. In re Kronig 190 USPQ; In re Pantzer 144 USPQ 415.

To argue that the instant combination is "unexpected", objective factual evidence supporting unexpectancy must be provided. In rebuttal of the *prima facie* cases of obviousness established by the examiner, evaluating and assigning weight to the evidence of nonobviousness, several factors must be kept in mind. The evidence must represent a comparison with the closest prior art. *In re Malagari*, 182 USPQ 549. Merely showing a difference in properties between the prior art and claimed invention is not enough. Any difference shown must be such that it would be considered unexpected by one of ordinary skill in the art. *In re Merck & Co. Inc.*, 231 USPQ 375; *In re Freeman*, 177 USPQ 139. The proffered evidence must be commensurate in scope with the claims, *In re Lindner*, 173 USPQ 356. Mere argument of variation by attorney without support in competent factual evidence is entitled to little probative value. *Ex parte Anderson* 21 USPQ2d 1258.

4. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Jan. 7, 2009

/Celia Chang/
Primary Examiner
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